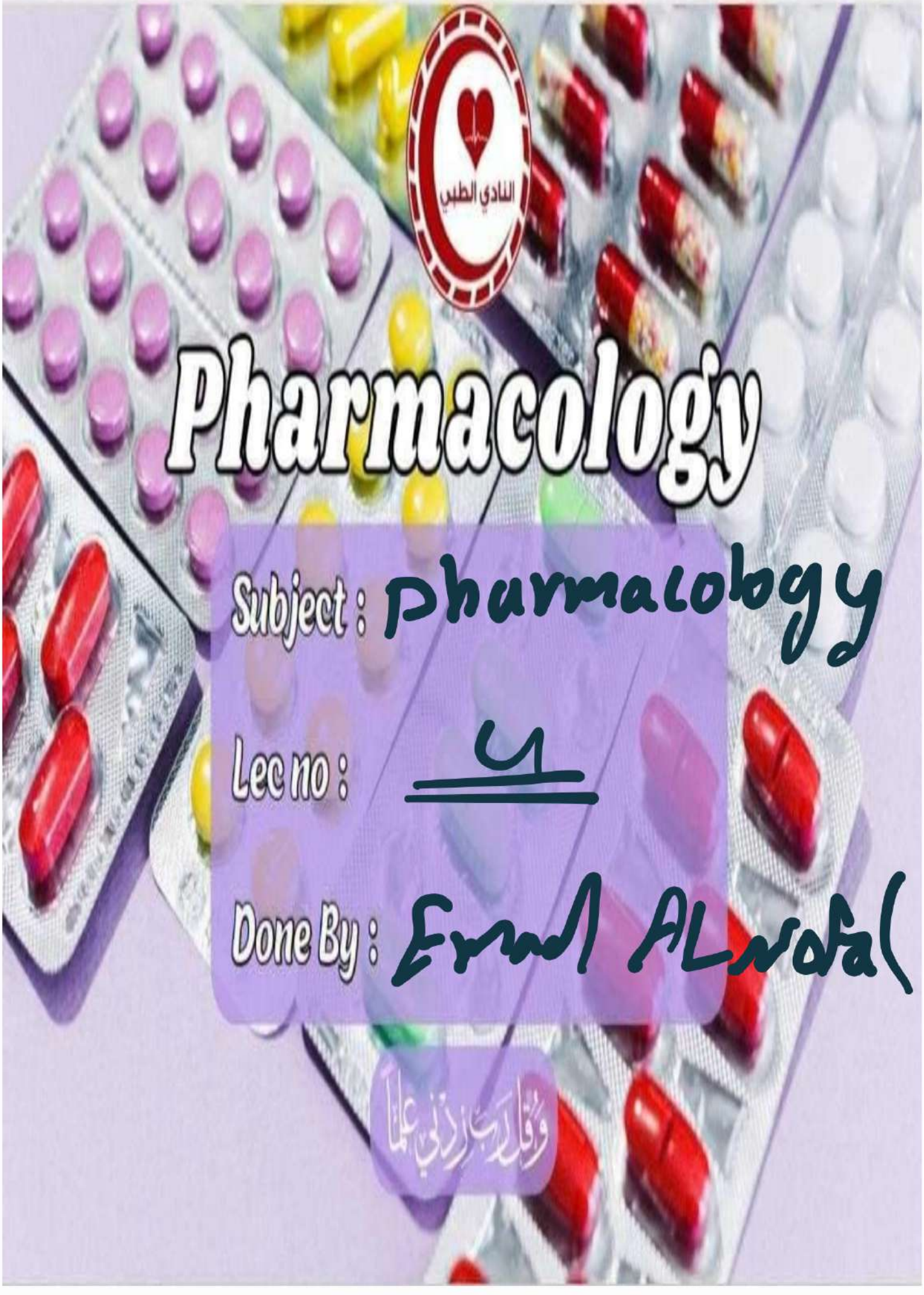
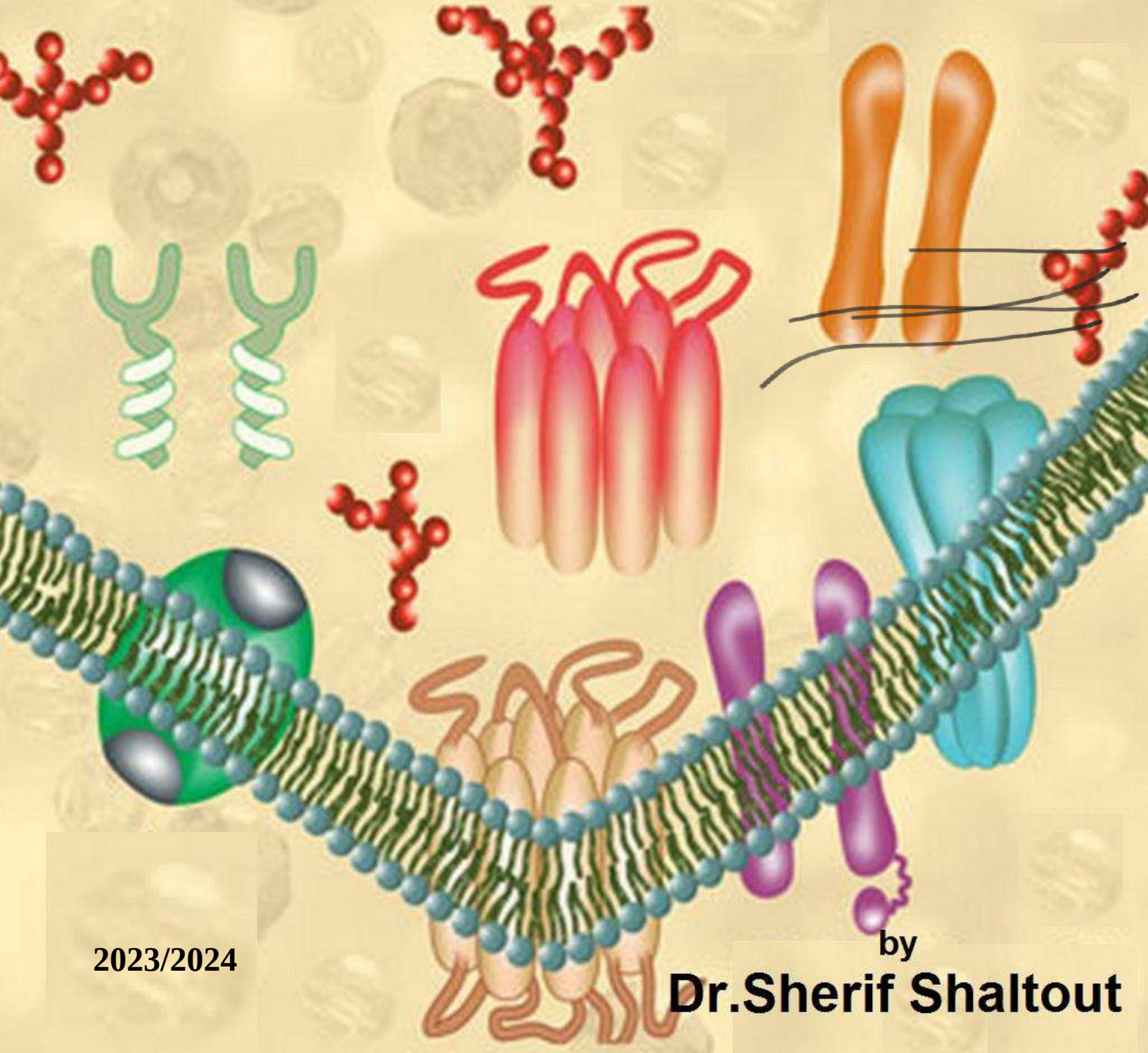

النادي الطبي
Pharmacology
Subject : pharmacology
Lec no : 4
Done By : Emad ALnofal
وقل رب زدني علما

# General Pharmacolog

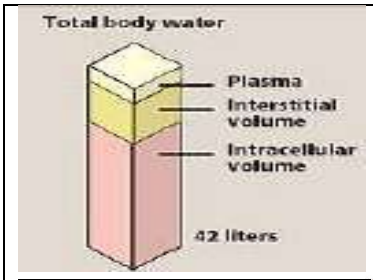


2023/2024

by
Dr.Sherif Shaltout

# DISTRIBUTION OF DRUGS

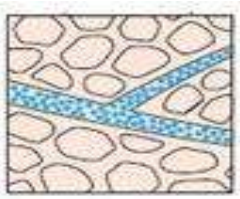
- It is the passage of drug through body compartments which are separated by capillary walls and cell membranes.
- Body fluid compartments:




1- **intravascular volume = 4 L/70 Kg**
2- **interstitial volume = 10 L/70 Kg**
**(Extracellular volume)**
3- **intracellular volume = 28 L/70 Kg**
***Total body fluid = 42 L/70 Kg**

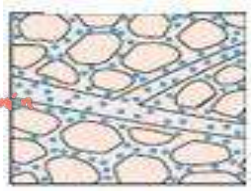
## Pattern of distribution:

### 1. Plasma compartment (one compartmental model):



- If a drug:
  - has a **high molecular weight** or
  - **binds strongly to plasma proteins**
- It is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment.
- e.g. Heparin , Dextran.

### 2. Extracellular fluid (two compartmental models):



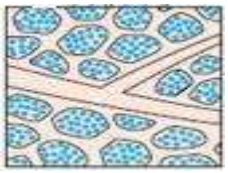
- If a drug has a **low molecular weight** and is **hydrophilic**
- It can move through the endothelial slit junctions of the capillaries into the interstitial fluid BUT cannot move across the lipid membranes of cells
- e.g. Aminoglycoside antibiotics, Mannitol.

### 3. Extra & intracellular fluid (multi-compartmental model)

- If a drug has a **low molecular weight** and is **lipophilic**
- It moves into the interstitium through the slit junctions and also moves through the cell membranes into the intracellular fluid.
- Some drugs uniformly distribute throughout whole body water e.g. Ethanol, sulphonamides.

Attached to cell compartment

- the majority of drugs distribute into several compartments, often binding cellular components for example, lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and within cells), or nucleic acids (abundant in the nuclei of cells)



4. **Tissue reservoir:** Drugs concentrated in certain tissues
   - **Iodine** in thyroid & salivary glands
   - **Calcium & tetracyclines** in bone & teeth
   - **Chloroquine** in liver
   - **Thiopental** in fat (Redistribution ??)

change in plasma drug concentration which alter the drug Action

## ❖ Volume of Distribution ($V_d$)

- Definition: the **apparent** volume of fluid required to accommodate the entire amount of the drug in the body in the same concentration as that present in plasma (i.e. when the drug is equally distributed between plasma and tissues).

If the Vd was 420L that mean I need 420 L to return the equilibrium between the Tissue and plasma

IF the Vd was high number it mean that the drugs reach the tissue

| $V_d$ (L) = | Amount of drug in the body |
|---|---|
| | Plasma concentration |
| | ( $V_d$ = A/C or Q/C) |

L/kg not

IF It X/kg you have to X in TBW

- The apparent volume of distribution does not describe a real, physical volume, but rather, reflects the **ratio of drug in the extraplasmic spaces relative to the plasma space** as it assumes that the drug distributes uniformly, in a single compartment, e.g. the Vd for digoxin is 6 **L/Kg** (in adult 70 Kg) or 420 **L**.

and if it is low number it still in the Plasma or ISF

4L → plasma

10 or 12 → ISF

- **Importance of $V_d$**

1. It is an estimate of the extent of **tissue uptake** of drugs:
   - Small $V_d$ (e.g. frusemide) indicates that tissue uptake is limited.
   - Large $V_d$ (e.g. digoxin) indicates extensive tissue distribution.

in plasma ISF

**2. In cases of drug toxicity**:

- Dialysis is **not useful** for **high $V_d$** drugs (most of drug is in the tissues).
- Dialysis is **useful** for **low $V_d$** drugs (most of drug is in the blood).

**3.** $V_d$ can be used to calculate the **loading dose (LD):**

**[LD = $V_d$ x $C_{ss}$** (Steady State plasma Concentration)]

**4.** $V_d$ can be used to calculate the **total amount of drug** in the body**:**

**[A = $V_d$ x $C_p$ ]**

## ❖ Factors Affecting Distribution of Drugs:

**1) Perfusion:** the amount of the drug which is delivered to a particular organ depends on the ***blood flow*** to that organ: ↑ blood flow → ↑ distribution.

**2) Diffusion:** the ability of the drug to diffuse across the cell membranes is governed by its ***lipophilicity***, ***ionization*** **&** ***molecular weight***: (as absorption)

**3) Binding to plasma proteins (PPs):**

- Most of drugs when introduced into the body are bound to plasma proteins (pp) e.g.

- **Albumin:** - the most important pp
  - Acidic & lipophilic drugs bind mainly with it
- **Other:** globulin, glycoprotein…etc

- Drug in blood exists in 2 forms: **free form** & **plasma protein bound form** which exist in equilibrium; when the free form is metabolized and/or excreted, another part is released from plasma proteins

| Free fraction | Bound fraction |
|---|---|
| • Active<br>• Diffusible<br>• Can be Metabolized<br>• Can be Excreted | • **In**active<br>• **Non**diffusible<br>• Can**not** be metabolized<br>• Can**not** be excreted<br>• Act as a reservoir for drug |

- **Significance of Binding to Plasma Proteins**

1. The binding of drug to plasma proteins **limits its tissue penetration & decreases its $V_d$.**
2. The bound drug cannot be eliminated → **prolongs the $t_{½}$** of the drug → **prolongs the effect** of drug.
3. **Hyboalbuminemia** e.g. starvation, malnutrition →**↑ free drug** → therapeutic dose changes to **toxic dose** e.g. phenytoin.
4. Competition for binding sites between drugs → **displacement of each other** → **clinically-significant drug interactions** e.g.

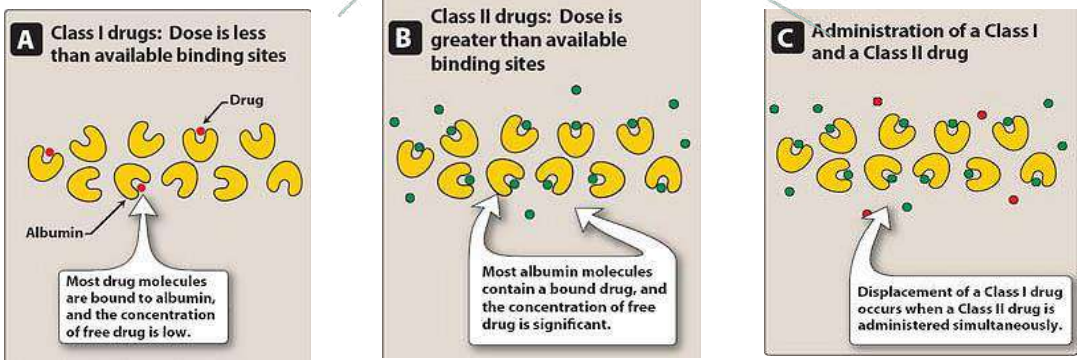
- Aspirin, sulphonamide displace warfarin → bleeding.
- Sulphonamide displaces bilirubin → kernicterus in premature neonates.

{When two drugs with high affinity for albumin are given, they compete for the available binding sites. The drugs with **high affinity** for albumin can be divided into two classes:

**1. Class I drugs:** If the dose of drug is less than the binding capacity of albumin i.e. **low dose/capacity ratio** → high bound fraction and **small free fraction**

**2. Class II drugs:** If the doses greatly exceed the number of albumin binding sites i.e. **high dose/capacity ratio → high free fraction**.

* When a patient taking a Class I drug, such as warfarin, is given a Class II drug, such as a sulfonamide antibiotic. Sulfonamide displaces warfarin from albumin, leading to a rapid increase in the concentration of free warfarin in plasma → ↑ therapeutic effects, as well as ↑ toxic effects → bleeding}



**4) Binding to cell and tissue constituents:**

- Drugs concentrated in certain tissues **(Tissue reservoir)**.

❖ **Passage across barriers:**

## Passage of Drugs to CNS

1. **Lipid-soluble** drugs pass freely through BBB, e.g. general anesthetics and other CNS depressants.
2. **3ry amines** can pass while 4ry $NH_4^+$ compounds (ionized) cannot.
3. **Some hydrophilic** antibiotics e.g. penicillin can pass **inflamed BBB** only

## Passage of Drugs to the Fetus

- Many drugs cross placental barrier by simple diffusion (depending on their lipid solubility & their degree of ionization) and can **harm the fetus:**
  - Drugs given in **3rd to 10th week** of pregnancy → **teratogenicity** e.g. thalidomide → phocomelia
  - Oral anticoagulants → fatal hemorrhage in the newborn.
  - Oral hypoglycemics (sulfonylureas) → prolonged neonatal hypoglycemia.
  - Aminoglycosides → 8th cranial nerve damage.
  - During labor, Morphine → respiratory depression (asphyxia neonatorum).

## Passage of drugs to breast milk

- Most of drugs administrated to lactating women are detectable in breast milk.
- pH of milk is more acidic (7.0) than that of plasma (7.4) → **basic drugs** accumulate in milk (ion trapping).
- Milk contains more fat than plasma → retention of **lipid soluble** drugs.

- **Drugs are contraindicated during lactation**:
  - Sedatives, hypnotics and narcotics → CNS depression in baby.
  - Oral penicillins and purgatives → diarrhea in baby.
  - Anticancer drugs → decrease growth of baby.
  - Bromocriptine & sex hormones → suppress lactation.